SEMI-OPIOID NALBUPHINE BASED NOVEL PHARMACEUTICAL APPROACHES FOR MANAGEMENT OF SEVERE PAIN

SYNOPSIS

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By

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INTRODUCTION

Pain is defined as a reflex withdrawal response to a noxious stimulus and response for essential reaction for obvious protective function even in the nonappearance of conscious perception. The pain sensation may lead to the circumvention of possibly harmful situations and injury (Michael J Hudspith, Philip J Siddall 2006). Pain has been defined by ***International Association For The Study Of Pain*** as ―an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage‖ (Garcia & Altman 1997). Pain is classified in many ways, as good or bad, necessary (requiring no treatment) or unnecessary (requiring treatment), organic or psychogenic, including its duration (acute, chronic), its pathophysiological mechanisms (physiologic, nociceptive, neuropathic), and clinical context like postsurgical, malignancy related, neuropathic or degenerative (Debebe Fikremariam 2011). Worldwide traumatic injury is the foremost cause of morbidity and death among all individuals in the age group of 45 years and below. Maximum traumatic injuries are due to motor vehicle accidents, gun shoot, homicide, war field situations, self-inflicted injury, or injury purposely inflicted by another person. The victims that survive from pain generally undergoes long term disability. Advances in medical technology continues to provide low mortality rates with respect to trauma, few number of patients develop pain beyond the acute phase and develop chronic post-traumatic post-surgical (PTPS) pain.

CLASSIFICATION OF PAIN

On the basis of duration of pain

Acute pain

It is defined as pain of current onset and probable limited duration. It usually has an identifiable temporal and casual relationship to injury or disease. It is associated with autonomic nervous system hyperactivity, including tachycardia, increased blood pressure, and anxiety (Garcia & Altman 1997). Ascending and descending mechanisms in the spinal cord and brain are thought to modulate pain as seen in (Figure 1.1). It is important to understand these neurobiological responses in order to appreciate the range of patients experiencing injury.

Chronic pain

It usually lasts longer than the time it takes for an injury to heal, and there is often no apparent explanation. Because of a tolerance to sympathetic hyperactivity and anxiety, patients with

chronic pain may not appear to be in pain and may lack the reactions seen in acute pain (Pamela E Macintyre, David A Scott, Stephan A Schug, Eric J Visser 2010)**.** Depression, functional disturbances such as withdrawal from social activities, and personality and life style changes are all objective clinical findings for chronic pain (Garcia & Altman 1997).

On the basis of pathophysiology

Physiologic pain

It is defined as swiftly perceived non-traumatic distress for short time period. Physiologic pain alarms the person towards the possibly injurious stimulus, such as a pointed or sharp object, and initiates withdrawal reflexes to prevent or curtail tissue injury. (Seminowicz & Davis 2006)

Nociceptive pain

Nociceptive pain is a harmful perception as a result of cellular damage followed by disease-related injuries, traumatic or surgical. The degree of tissue damage and the production of inflammatory proteins are connected to the level of nociceptive pain. (Osawa & Aruga 2017)

Neuropathic pain

It is demarcated as pain caused by a dysfunction or pathologic lesion‖ in CNS and nerves. Neuropathic pain is a result of dysfunction of the peripheral or central nervous system (CNS) due to any of potential damage caused either: Compression, Metabolic injury, Infiltration, Transaction, Ischemia (Haanp et al. 2011)

Injury or physical trauma results in substantial damage to the tissue and cells of body and evoke a painful condition. (Gao et al. 2013) The pain management has always been a concern and a challenge to the medical fraternity when it comes to pre-hospitalization level during war or battlefield scenario or any other surgical or orthopedic trauma. In order to provide fast relief from severe pain, parenteral opioids are administered during the hospitalization under the supervision of medical staff. It is therefore very imperative to have a non-injectable technique that can deliver the drug into the systemic circulation for rapid onset of action. The thesis work primarily focusing on preparation, evaluation and optimization of various nano formulations of nalbuphine and to explore their prospective role in mimicking pain (unpleasant sensation). Formulations such as pulmonary Nanoparticle (NPs), nasal Solid Lipid Nanoparticle (SLN), submental, chitosan NPs are mainstay treatment approaches undertaken in this notion to attenuate painful conditions. Rationale behind

selection of non-invasive routes is that they are competent enough to cross the BBB barrier and deliver the drug at kappa receptors in brain and spinal cord. This leads to generation of central as well as peripheral analgesic action. As Nalbuphine drug is kappa agonist and mu antagonist, effective in producing analgesic action with no respiratory depression or any other kind of adverse effect (those generally encountered in morphine and its analogues).

The work focuses on several routes i.e. (nasal, submental, pulmonary delivery) to deliver the drug effectively for pain management with negligible side effects. The major approach throughout the development of formulation was to fabricate and optimise nanoparticle of drug using either lipids or mucoadhesive agents. Further, the characterization of the developed nanoparticles for their size, morphology, release profiles from the formulation, was performed then *in vivo* studies including toxicity, efficacy and Pk studies in animals along with establishing a proof of concept (POC) in human volunteers using gamma scintigraphy.

RESEARCH GAP

- Formulate and optimize nalbuphine Hcl nanoparticles for Pulmonary delivery using dry powder inhaler for pre hospital management of acute pain
- To explore novel submental route of delivery nalbuphine in ameliorating acute pain in pre hospital emergent condition and also to establish a comparative profile study with intramuscular route.
- To Formulate and optimize nalbuphine base loaded mucoadhesive nanosuspension for direct delivery to brain through intranasal for instant pain management.
- In-Silico Prediction of relevant carrier for delivery of nano formulation of nalbuphine for management of pain
- Formulation and optimization of nalbuphine base loaded solid lipid nanoparticles for sustained delivery through intranasal route to manage pain.
- Explore effect of Nalbuphine in cisplatin induced neuropathic pain & its mechanistic action on experimental animal model.

MOTIVATION:

Pain Shock & Death

- Extreme pain causes neurogenic shock by overexciting the parasympathetic nervous system
- This results in a decrease in heart rate which in turn decreases the pulse and leads to a dangerous drop in blood pressure.
- As per U.S military data the majority of military personnel death is due to pain and shock

MANAGEMENT OF PAIN/ TREATMENT OPTIONS AVAILABLE

The management of various types of pain i.e. postoperative, cancer, acute, inflammatory or neuropathic is the most common issue come across by pharmacological experts and clinicians. The first approach by all medical experts is to treat pain raised due to any cause. Depending upon its severity pain in the pre-hospital environment the treatment could be given in number of ways. Treatments used included intravenous or oral morphine, hydromorphone, fentanyl, oxycodone, tramadol, inhalational nitrous oxide and oxygen (Entonox),(Fening 2020) local anaesthetics, anticonvulsants, paracetamol (acetaminophen), cannabinoids and adjuvant analgesics such as gabapentine and Pregabalin, ketamine and others (nefopam).(Guindon J, Walczak JS 2007)

Why Alternate Route is needed?

After I.V. administration, peak plasma concentration is achieved within 1-2 min. But in case of mass causalities medical or paramedical staff is required for iv administration, and these if at all present, will not be in a sufficient number in places far distant from the hospitals. Alternatively, intramuscular auto-injectors could be employed, but the route is not particularly fast, and autoinjectors are nor freely available. A Buddy Care is required to deal with emergency situation, particularly with reference to military or paramilitary situations.

SCOPE OF THE WORK

In the past few decades, attitudes towards pain have drastically changed from the antiquated view. The realisation that pain is a disease state of the nervous system, rather than merely a symptom of illness or damage, has probably been the most significant development in medical views about pain science. In a war scenario, where there is a mass causality or the incidences where managing pre hospital pain is a major challenge. Extreme pain induces neurogenic shock by overexciting the parasympathetic nervous system, and there is a connection between pain, shock, and death. This causes a substantial reduction in heart rate (bradycardia), which lowers the pulse and causes a hazardous drop in blood pressure. If it is untreated it can be life threatening, as per U.S military data the majority of military personnel death is due to pain and shock.

Since then, morphine and other opioid medications have played a critical role in pain treatment in harsh environments, notably in the military. Undoubtedly the pre- eminence and success rate of opioid drugs in management of pain is very high. However, their use has advantage and also results in significant side effects, the use of Opioid in austere environments is further intricated by international governing regulations for use of opioids drugs. Despite these shortcomings, opioids especially morphine has basically been the gold standard drug to which other drugs are compared to treat pain in raucous conditions. In the beginning, the knowledge of pain mechanisms and related morbidity is still in its infancy. Furthermore, pain treatment options other than morphine (e.g., adjunct treatments, drug delivery methods and novel medicines) are becoming more popular. Pain relief on the battlefield depended on the speed and dexterity with which doctor/surgeon of the time could operate.

Nalbuphine (NLB) is a powerful analgesic with an analgesic efficacy similar to morphine (0.8 to 0.9 times). When given in similar amounts, nalbuphine and morphine are regarded to be equally powerful. For example, 20 mg of nalbuphine is the same as 20 mg of morphine. It can be given through subcutaneous (SC), intravenous (IV), intramuscular (IM) routes of injection, which in turn define its onset of action. Nalbuphine action initiates within 30 min of intramuscular (IM) or subcutaneous administration and less than 5 min of intravenous injection. Nalbuphine does not get absorb from GIT so addiction of the drug is not possible also it has ceiling effect at higher dose whereas morphine causes respiratory depression. With perceptible advantage of nalbuphine over morphine in terms of side effects and low addiction therefore, it seemed logical to us to formulate formulation, with minimum side effects which could be deliverable in the pre-hospital or field scenario. Therefore, there is a need to develop novel

nalbuphine formulation that are more effective, cost- effective to ensure availability at a mass scale and buddy care approach than the existing ones for managing pain. (Aitkenhead et al. 1988).

The thesis has been designed with the following broad scope and specific objectives as under:

OBJECTIVES OF THESIS

- Formulate and optimize nalbuphine Hcl nanoparticles for Pulmonary delivery using dry powder inhaler for pre hospital management of acute pain
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- *In-silico* Prediction of relevant carrier for delivery of nano formulation of nalbuphine for management of pain
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Thesis Organization:

In this thesis, we have tried to address all the research gaps in eight chapters with existing literature. This thesis aims to address major issues concerning to the cost effective fabrication of the nanoformulation and the novel approaches through which the rapid onset of action could be achieved. The focus was more towards developing formulations and approaches for buddy care with its application more towards field conditions. The thesis has been organized describing the need for the study, present state of art followed by experimental investigations and their analysis as follows:

Chapter-1 gives a general insight into pain, types of pain, how pain perception take place with a brief discussion on various routes and approaches by which the bottleneck could be avoided .The chapter also provide the ideal characteristics for Prehospital Analgesic Agent with limitation and improvement required in the real field scenarios. The chapter concluded by defining the research problem and highlights the importance of present work followed by the hypothesis made in the current development.

Chapter-2: *Discuss about* Pulmonary delivery, the work emphasizes on preparation of Nalbuphine nanoparticles by nano-precipitation method. This work successfully describes the parameter optimization to obtain nalbuphine nanoparticles, characterization of developed nanoparticles, and deposition of nano vs parent-micronized form of drug using Anderson cascade impactor, in vivo toxicity studies in animal model followed by ventilation scintigraphy in healthy human volunteers. The scintigraphy study focus on its percent deposition in lungs and time required for systemic availability of the drug through absorption from the lungs. Nano Nalbuphine was developed with characteristics favoring deeper penetration and absorption in systemic circulation through lungs. There was a significant improvement in respirable fraction with nalbuphine pulmonary nanoformulation in favor of better lung deposition as compared with the micronized one.

Chapter-3: A new route to deliver nalbuphine, known as submental route was explored for the first time to deliver nalbuphine as an analgesic in pre hospital scenario. Submental delivery (S.M) refers to a method of administering a drug in submental region i.e. fascial space of the head and neck. It is a potential space located between the mylohyoid muscle superiorly, the platysma muscle inferiorly, under the chin in the midline. High vascularity facilitates rapid drug absorption directly into the venous circulation through the anterior jugular veins, bypassing the gastrointestinal tract, the hepatic portal circulation, and hepatic first-pass metabolism. In this

study, we optimized the injectable dose in animal model and performed toxicity studies along with efficacy studies using Eddy's hotplate. Further to prove the systemic bioavailibity of the drug, gamma scintigraphy technique was used in which the drug was tagged with 99m Technetium and was injected in animal through submental route. Submental delivery was compared with intramuscular route in animals by administration of radiolabeled drug through intramuscular route. It was found that the drug reached the systemic circulation within 5 min of administration in case of submental delivery resulting in quick onset of action whereas the intramuscular route took 15-20 min to get into systemic circulation. A rapid clearance from the site was observed with submental delivery whereas a slow clearance was seen during intramuscular delivery. The results obtained from animals also, where Tc-DTPA was injected into the submental space and compared with intramuscular. Both the results from animal and human suggested that submental site offers rapid absorption into the systemic circulation compared to conventional intra-muscular route.

Chapter-4: This chapter discuss about incorporation o*f in-silico* studies *for s*creening of best suitable excipients was done by bioinformatics approach, various software were used where docking of excipients with drug was simulated to evaluate the stability and ability of docked complex (drug-carrier) to reach Blood brain barrier (BBB). Upon the screening, we found that phosphatidylcholine is the best suitable for our purpose of sustain delivery.

Chapter-5: The intranasal formulation for nalbuphine was formulated for sustained drug delivery to the brain. With phosphatidylcholine as a lipid carrier based on the *in-silico* studies, the optimization of solid lipid nanoparticle (SLN) formulation was carried out using QbD. The optimized formulation was then characterized for particle size, morphological studies, permeation through goat nasal mucosa, toxicity and efficacy studies in animal model using hot plate. The results obtained illustrated that the chosen formulation was able to release the drug for 8hrs. Fabricated SLN formulation was capable of delivering the drug to the brain, which was confirmed by conducting gamma scintigraphy studies.

Chapter-6: For faster onset of action, a nanosuspension containing nalbuphine loaded chitosan nanoparticles were developed using ionic gelation method. A morphological study using SEM & TEM supported the suitability for intranasal administration and was in accordance to the results obtained in the dynamic light scattering. The nanosuspension developed was administered through intranasal route for direct nose to brain delivery of nalbuphine for faster onset of action. Biodistribution study in mice showed the rapid and high concentration uptake

of drug in the brain post administration through intranasal delivery. A comparative profile between intranasal and intramuscular delivery was carried. It was found that with intramuscular delivery, delivery to brain was low and maximum drug deposited was in kidney, liver, spleen. The results obtain from gamma scintigraphy in rabbit confirmed that intranasal route delivers nalbuphine to the brain rapidly and effectively. The nose to brain delivery directly delivers the drug to be brain bypassing blood brain barrier and due to nano size, the delivery becomes more effective.

Chapter-7: We extended the use of this formulation in treating neuropathic pain. The results obtained through molecular study experiments on brain tissue after intranasal delivery of nanosuspension illustrated that there was decrease in the protein expressions and markers, which became up regulated during neuropathic pain in animal model. The efficacy of nalbuphine in ameliorating this condition was due to its kappa agonist activity and similar inhibition of other markers of different signaling cascade thereby exerting potent antioxidant and anti-inflammatory activity. The Intranasal delivery route can serve as a non-invasive buddy care and shall be very useful in management of pain in field conditions. The developed formulation and intranasal route opens new avenues in management of pain, as do the submental route and pulmonary route for delivery of nalbuphine to the patient suffering from acute pain (explosion / bullet / burn / fracture injury, for e.g.) for fast action in pre-hospital zone.

Chapter-8 deals with the conclusion drawn from the entire work along with some recommendations for future work.

LIST OF PUBLICATION FROM THESIS

1. **Kushagra Khanna,** Ritu Karwasra, Sandeep Choudhary, Deeksha Sharma, Nitin Sharma, Puja Nagpal, Varsha Chorsiya, Dhruv Kumar Nishad, Harvinder Popli, Aseem Bhatnagar. Submental nalbuphine exhibits improved efficacy in ameliorating acute pain in prehospital emergent conditions; a comparative study with conventional intramuscular using gamma. **Journal of Injury (2020) (I.F: 2.5)**

2. **Kushagra Khanna,** Nitin Sharma, Sonalika Rawat, Nazia Khan, Ritu Karwasra, Nazeer Hasan, Abhishek Kumar, Gaurav Kumar Jain, Dhruv Kumar Nishad, Sakshum Khanna, Harvinder Popli, Aseem Bhatnagar. "Intranasal solid lipid nanoparticles for management of pain: A full factorial design approach, characterization & Gamma Scintigraphy" **Chemistry and Physics of Lipids**. **May 2021 (I.F 3.32)**

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